SYNOPSIS

Issue Date: 27 February 2013

Name of Sponsor/Company	Janssen Korea Ltd.
Name of Finished Product	Fentanyl
Name of Active Ingredient	fentanyl

Protocol Number: FEN-KOR-10

Title of Study: Evaluation in Efficacy and Safety of Fentanyl-TTS (Durogesic® D-Trans) for Treatment of Chronic Pain

Study Name: Evaluation of efficacy and safety of Fentanyl-TTS (Durogesic®D-TRANS) in chronic pain / FEN-KOR-10

NCT Number: N/A

Clinical Registry Number: CR002155

Principal Investigator: Sang-Ryong Jeon (Asan Medical Center, Department of Neurosurgery, 388-1 Pungnap-2-dong, Songpa-gu, Seoul)

Study Centers: A total of one institution participated in the clinical study.

Publication (Reference): Acta Neurochir (2011) 153:181−190

Study Period: It was conducted from 24 October 2005 to 13 November 2006.

Phase of Development: Phase 4 Clinical Trial

Objectives: This study was to confirm effectiveness and safety of Durogesic® D-Trans, the opioid agent, for chronic pain in subjects with chronic non-cancer pain and to find out usefulness of Durogesic® D-Trans for management of chronic pain by evaluating functionality in subjects by pain intensity.

Methodology: This study was a prospective, open-label study of Durogesic® D-Trans in subjects complaining of chronic non-cancer pain, conducted for 12 weeks. Efficacy and safety were evaluated at Week 1, Week 4, Week 8 and Week 12 visits.

Number of Subjects: The total sample size planned in this study was 52, but actually 65 subjects were included in the safety population, 56 in the FAS population, and 40 in the PP population.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Subjects complaining of spine-related and extremity pain lasting for 3 months or longer,
- Subjects with pain with Numeric Rating Scale (NRS) at 4 or higher in the past 72 hours,
- Subjects in 19 years of age or older,
- Subjects with good overall health condition based on the following criteria
    - Medical history and medication history,

  - Physical examination prior to the treatment,
  - Vital sign: Blood pressure and pulse,
  - Clinical laboratory tests: Clinical laboratory measurements within double of normal range,

    (Hepatic function: Within double of normal range for SGOT/SGPT, Renal function: Creatinine not exceeding 2.0ml/dl)

- Subjects who were fully capable to communicate with the clinical investigators about their pain,
- Subjects who could use appropriate contraception in case of childbearing potential during the study period,
- Subjects who signed the informed consent form.

Exclusion Criteria:

- Subjects participating in other clinical trial,
- Subjects with history of hypersensitive reaction to narcotic analgesics,
- Subjects with history of narcotic abuse,
- Subjects with serious psychotic disorder,
- Subjects who were unable to use transdermal analgesics due to a dermatological condition,
- Subjects with history of CO_2 retention (e.g., chronic obstructive pulmonary disease),
- Subjects who had received surgery, which might affect pain, in the area with pain within 7 days prior to initiation of the clinical study,
- Subjects with significant disease which could have a serious influence on conduting or interpreting the results of the clinical study,
- Subjects with potential to complain of unnecessary pain due to insurance problem such as car accident.

Duration of Treatment: The duration of the clinical study was for up to 12 weeks.

Criteria for Evaluation:

Efficacy Evaluation:

- Primary Efficacy Endpoint
  - The Percent change in pain intensity prior to study treatment (Day 0) and after study treatment (Week 12)
- Secondary Efficacy Endpoints
  - Dose of study medication prescribed at each day of evaluation
  - Functionality and sleep in subjects examined at each day of evaluation
  - Satisfaction in study medication by subjects and investigators

Safety Evaluation:

- Adverse events

Statistical Methods:

Sample Size Determination:

For the sample size in this study, 41 subjects were required at 2.5% of one-sided sigmificance level and 90% power when hypothesizing 30% of the percentage of patients with pain intensity decreased by 50% or more and 10% of natural decreasing rate, and it was planned to recruit 52 subjects considering 20% of dropout rate.

Analysis Population Criteria:

The results were analyzed for the FAS (Full analysis set) population and PP (Per-Protocol) population.

Statistical Analysis Methods:

The primary efficacy endpoint of the study was %PID (Pain Intensity Difference), and the percent change was calculated and the percentage of subjects with pain intensity decreaed by 50% or more and its 95% confidence interval were presented. In addition, it was indicated whether there was statistically significant change in each of the percent change and changes in pain intensity after fentanyl administration, using Wilcoxon signed-rank test.

For the secondary endpoints, descriptive statistics were presented for dose of study medication prescribed at each day of evaluation and satisfaction in functionality and sleep by subjects examined at each day of evaluation by visit, and descriptive statistics were presented and statistical test was performed for the changes from baseline to the study end point as to the change in pain intensity which was the primary efficacy endpoint. In addition, satisfaction in study medication by subjects was summarized.

Adverse events were summarized descriptively by system organ class and preferred terms. Overall adverse events, overall adverse drug reactions, serious adverse events, non-serious adverse events, non-serious adverse drug reactions, and adverse events causing study discontinuation were described. In addition, severity, causal relationship, measures taken, and outcome by adverse event were examined.

Results:

Study Population:

A total of 65 subjects participated in this study, and 24 subjects (36.92%) of them were withdrawn from the study without completing the clinical study as per the study protocol. The reasons for withdrawal included adverse events in 19 subjects (29.23%), subject choice in 4 subjects (6.15%), and lack of efficacy in one subject (1.54%). 41 subjects (63.08%) completed the clnical study.

Information about Completed/Withdrawn Subjects (FEN-KOR-10)

	N	(%)
Subjects with informed consent	65	
Subject who completed the study	41	(63.08%)
Subjects withdrawn	24	(36.92%)
Adverse events	19	(29.23%)
Subject choice	4	(6.15%)
Lack of efficacy	1	(1.54%)

All of the total enrolled 65 subjects received the study drug at least once and were included in the safety population, and 56 subjects who were evaluated for the primary endpoint (pain intensity) from the initial visit to all the following visits without violating the inclusion/exclusion criteria were included in the FAS population and 40 subjects excluding subjects with protocol deviations and withdrawal were included in the PP population.

Number of Subjects in FAS and Safety Analysis Populations (FEN-KOR-10)

	N	(%)
Subjects with informed consent	65	
FAS (Full analysis set) Population	56	(86.15%)
PP (Per-Protocol) Population	40	(61.54%)
Safety (Safety analysis set) Population	65	(100.00%)

Efficacy Results:

The primary efficacy endpoint in this study was the percent change in pain intensity evaluating the percentage of subjects with PID decreased by 50% or more. Among them, it was revealed that the percentage of subjects with PID of pain intensity in average for 72 hours at 50% or more was 64.29%, the percentage of subjects with PID of pain intensity at resting at 50% or more was 67.31%, and the percentage of subjects with PID of pain intensity in motion was 53.57%. Moreover, the percent change in pain intensity from baseline to final evaluation decreased by 53.22% (in average), 53.93% (at resting), and 48.61% (in motion), respectively, showing statistically significant decrease in pain symptom.

Results in Primary Efficacy Endpoint (%PID) (FAS)

						%PID≥0.5		
	N	**Mean ± SD**	**Median**	**Min ~ Max**	**p-value***	**n**	**%**	**95% CI**
Pain intensity in average	56	53.22 ± 25.30	53.57	0.00 ~ 100.00	<.0001	36	64.29	(50.84 ~ 77.73)
Pain intensity at resting‡	52	53.93 ± 29.12	60.00	-20.00 ~ 100.00	<.0001	35	67.31	(53.60 ~ 81.02)
Pain intensity in motion	56	48.61 ± 28.62	50.00	-25.00 ~ 100.00	<.0001	30	53.57	(39.62 ~ 67.01)

* Wilcoxon signed-rank test
** Number of subjects with the percent change in pain intensity at 50% or more
%PID = (NRS(baseline)-NRS(end point))/NRS(baseline)*100
‡ Excludiong 4 subjects (FAS) with 0 at baseline for pain intensity at resting in the past 72 hours.

Among the secondary endpoints, it was indicated that there was a statistically significant increase of change in dose of the study drug and there were also statistically significant improvements in change of scores for influencing daily life, walking, meal intake and mood regulation with respect to change in functionality assessment cause by pain.

Change in Major Efficacy Endpoints by Parameter (FAS)

Parameter	N	Mean ± SD	Median	Min ~ Max	p-value*

Parameter	N	Mean ± SD	Median	Min ~ Max	p-value*
Dose of study drug†	51	22.33 ± 16.71	25.00	-1.74 ~ 62.50	<.0001
Evaluation of daily life	43	-4.23 ± 2.17	-5.00	-9.00 ~ 1.00	<.0001
Evaluation of walking	43	-3.72 ± 2.55	-3.00	-9.00 ~ 3.00	<.0001
Evaluation of food intake	43	-2.98 ± 2.91	-3.00	-10.00 ~ 3.00	<.0001
Evaluation of mood regulation	43	-4.58 ± 2.39	-5.00	-9.00 ~ 3.00	<.0001

* Wilcoxon signed-rank test
† Baseline value (Visit 1 ~ Visit 2)

Moreover, it was shown that the percentage of subjects not awaken due to pain during the sleep increased from 37.50% (Week 0) to 89.19% (Week 12) for change in evaluation for sleep in the FAS population. With respect to evaluation for satisfaction in treatment by investigators and subjects, it was revealed that the percentage evaluated as "very satisfactory" or "satisfactory" at Week 12 after study treatment was 86.49% by investigators and 94.59% by subjects, and 93.02% of subjects indicated satisfaction in study medication at final visit as very satisfactory or satisfactory, indicating that the most dominant reason for the satisfaction was "excellent efficacy in pain treatment."

Safety Results: Among total 65 subjects who participated in the clinical study and received the study drug at least once, a total of 55 subjects (84.62%) experienced 134 adverse events, including nausea (49.23%), diziness (43.08%), somnolence (30.77%), constipation (16.92%), vomiting (15.38%), pruritus (13.85%), edema (6.15%), dyspepsia (3.08%), and decreased appetite (3.08%), and 52 subjects (80.00%) experienced 122 adverse drug reactions. Serious adverse events occurred in 2 subjects (3.08%) with two events (inadequate analgesia and hypoglycemia), and no death was reported.

Summary of Adverse Events (N=65)

	Number of Subjects	(%)	Number of Events
Adverse events	55	(84.62%)	134
Adverse drug reactions	52	(80.00%)	122
Serious adverse events	2	(3.08%)	2
Death	0	(0.00%)	0

Safety evaluations based on clinical laboratory tests, physical examinations, vital signs and electrocardiograms were not performed.

Study Limitation: Because the design of this study is a single-arm study having limitation in interpretation, a caution is required to determine that the efficacy evaluation based on changes before and after the administration of the study drug has been caused only by fentanyl administration. In addition, the limitation was shown for evaluating the efficacy of pain control when considering that the number of subjects participating in the clinical study was small and the considerable number of subjects took concomitant analgesics.

Conclusion: Based on continuous improvement in pain and improvement in functionality and sleep demonstrated in subjects complaining of chronic non-cancer pain after administering fentanyl, it is considered that treatment with fentanyl in subjects complaining of chronic non-cancer pain improves quality of life as well as pain in patients.

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